Research paper

The protective effect of sodium-glucose cotransporter 2 inhibitors and the incidence of ovarian cancer: a nationwide cohort preliminary study

Keywords
epidemiology, type 2 diabetes mellitus, ovarian cancer, duration, SGLT2 inhibitors

Abstract

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are commonly used antihyperglycemic medications that also exhibit anti-inflammatory and antioxidant effects. Ovarian cancer, a common gynecological neoplasm, is associated with increased inflammation and oxidative stress. Thus, this study investigated the correlation between the usage of SGLT2 inhibitors and the incidence of ovarian cancer in the population with type 2 diabetes mellitus (T2DM).

Material and methods

A retrospective cohort study was conducted, and patients with T2DM were divided into those who used SGLT2 inhibitors and those who did not. A total of 163 668 and 327 336 patients with T2DM were categorized into the SGLT2 inhibitor and control groups, respectively. The primary outcome was the development of ovarian cancer, as identified using diagnostic codes and laboratory examination findings. Cox proportional hazard regression was adopted to yield the adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for ovarian cancer events between the two groups.

Results

A total of 167 and 222 patients developed ovarian cancer in the SGLT2 inhibitor and control groups, respectively. The incidence of ovarian cancer was significantly lower in the SGLT2 inhibitor group than in the control group (adjusted hazard ratio: 0.73, 95% CI: 0.60-0.89, $P = 0.0023$). Subgroup analysis stratified by oral medications revealed that the effect of SGLT2 inhibitors on ovarian cancer development was significantly different from those of biguanides, sulfonylureas, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors ($P < 0.05$).

Conclusions

This preliminary study showed that the administration of SGLT2 inhibitors in patients with T2DM is associated with a lower incidence of ovarian cancer.

The protective effect of sodium-glucose cotransporter 2 inhibitors and the incidence of ovarian cancer: a nationwide cohort preliminary study

Abstract

Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are commonly used antihyperglycemic medications that also exhibit anti-inflammatory and antioxidant effects. Ovarian cancer, a common gynecological neoplasm, is associated with increased inflammation and oxidative stress. Thus, this study investigated the correlation between the usage of SGLT2 inhibitors and the incidence of ovarian cancer in the population with type 2 diabetes mellitus (T2DM).

Material and Methods: A retrospective cohort study was conducted, and patients with T2DM were divided into those who used SGLT2 inhibitors and those who did not. A total of 163 668 and 327 336 patients with T2DM were categorized into the SGLT2 inhibitor and control groups, respectively. The primary outcome was the development of ovarian cancer, as identified using diagnostic codes and laboratory examination findings. Cox proportional hazard regression was adopted to yield the adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for ovarian cancer events between the two groups.

Results: A total of 167 and 222 patients developed ovarian cancer in the SGLT2 inhibitor and control groups, respectively. The incidence of ovarian cancer was significantly lower in the SGLT2 inhibitor group than in the control group (adjusted hazard ratio: 0.73, 95% CI: 0.60-0.89, $P = 0.0023$). Subgroup analysis stratified by oral medications revealed that the effect of SGLT2 inhibitors on ovarian cancer development was significantly different from those of biguanides, sulfonylureas, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors ($P < 0.05$).

Conclusions: This preliminary study showed that the administration of SGLT2 inhibitors in patients with T2DM is associated with a lower incidence of ovarian cancer.

Keywords: SGLT2 inhibitors; epidemiology; ovarian cancer; duration; type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is among the most prevalent diseases globally and is characterized by increased blood glucose levels [1]. The primary pathophysiological mechanism underlying chronic hyperglycemia and T2DM is the endogenous resistance of body cells to insulin [2]. Treatment for T2DM typically involves oral medications, such as biguanides and alpha-glucosidase, and insulin injections are required for refractory T2DM cases [3]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have become increasingly popular in T2DM treatment because of their ability to reduce hyperglycemia by approximately 0.5% to 1.0% which is the primary and most crucial mechanism of SGLT2 inhibitors [4, 5]. In another previous study, the combined application of SGLT2 and DPP-4 inhibitors resulted in a 0.71% greater reduction in the glycated hemoglobin level than did DPP-4 inhibitor monotherapy [6].

In addition to having an antihyperglycemic effect, SGLT2 inhibitors exert a protective effect on other areas of the body [4, 7], and SGLT2 inhibitors can reduce the incidence of several diseases [8-11]. SGLT2 inhibitors were discovered to be beneficial for managing cognitive impairment [12]. Furthermore, patients with T2DM using SGLT2 inhibitors were discovered to have a substantially lower incidence of myocardial infarction than that of those not using such inhibitors [8]. SGLT2 inhibitors also exert renoprotective effects, including improving the glomerular filtration rate [9]. Furthermore, population-based studies have indicated that the use of SGLT2 inhibitors can reduce the incidence of eye disorders, such as dry eye disease and diabetic retinopathy [10, 13, 14]. In addition, SGLT2 inhibitors were reported to exert an anti-inflammatory effect by regulating proinflammatory cytokine expression [7]. For example, SGLT2 inhibitors were demonstrated to suppress inflammatory reactions in an experimental model of autoimmune myocarditis [15]. SGLT2 inhibitors were also reported to possess antioxidant properties, as evidenced by a decrease in reactive oxygen species production following the application of SGLT2 inhibitors in an animal diabetic kidney disease model [16]. Moreover, an experimental study indicated that SGLT2 inhibitors reduced oxidative stress and myocardial fibrosis [17].

Ovarian cancer is the second most common gynecological cancer and has a 5-year survival rate of 47.4% [18]. The known risk factors for ovarian cancer include delayed childbearing, early menarche, a family history of ovarian cancer, and preexisting endometriosis [19]. Ovarian cancer is more likely to develop in individuals with hyperglycemia and T2DM [20], and the mortality rate of ovarian cancer is considerably higher in the T2DM population [21]. The development of ovarian cancer is associated with inflammation, as evidenced by increased levels of interleukins and tumor necrosis factor in patients with ovarian cancer [22]. Furthermore, oxidative stress is strongly associated with the pathogenesis and neoangiogenesis of ovarian cancer [23]. A higher reactive oxygen species level is correlated with metastasis and therapy resistance in ovarian cancer [24]. Still, few studies have evaluated the correlation between the use of SGLT2 inhibitors and the incidence of ovarian cancer, despite SGLT2 inhibitors being able to suppress inflammation, which is a key mechanism in the development of ovarian cancer [16, 22].

The present study investigated the potential protective effect of SGLT2 inhibitors on the development of ovarian cancer by using data from Taiwan's National Health Insurance Research Database (NHIRD). In addition, this study analyzed the effects of SGLT2 inhibitors on patients with T2DM with different characteristics.

Materials and Methods

Data Source

The current study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. The study was approved by Chung Shan Medical University Hospital. The requirement for written informed consent was waived by both institutions. The NHIRD contains claims data for 23 million Taiwanese individuals, with the data covering the period from January 1, 2000, to December 31, 2021.

Patient Selection

This was a retrospective cohort study. Patients with T2DM using SGLT2 inhibitors who met the following criteria were selected: (1) having a diagnosis of T2DM based on *ICD-9-CM* or *ICD-10-CM* codes between 2015 and 2021; (2) visiting an internal or a family medicine physician for more than 3 months; (3) undergoing a glycated hemoglobin examination prior to the T2DM diagnosis; and (4) receiving a prescription for SGLT2 inhibitors, such as dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin, as identified using ATC codes. The index date for this study was defined as 6 months after the initial SGLT2 inhibitor prescription. The following exclusion criteria were applied to standardize the T2DM population: (1) absence of demographic data, (2) use of antidiabetic medication before the T2DM diagnosis, (3) age of younger than 20 years or older than 100 years, and (4) diagnosis of any gynecological cancer before the index date. Propensity score matching (PSM) was used to match the SGLT2 inhibitor group with a control group, with demographics, systemic covariates, and associated medications considered. After PSM, 136 245 patients with T2DM were included each in the SGLT2 inhibitor group and in the control group. Figure 1 presents the flowchart of patient selection.

Main Outcome

The primary outcome in this study was the development of ovarian cancer, defined on the basis of the following criteria: (1) receiving a diagnosis of ovarian cancer based on *ICD-9-CM* or *ICD-10-CM* diagnostic codes; (2) receiving a pelvic examination before or at the time of the ovarian cancer diagnosis, as indicated by procedure codes; (3) undergoing a computed tomography scan, pelvic ultrasound exam, or cancer antigen 125 (CA-125) test before or at the time of the ovarian cancer diagnosis, as indicated by procedure codes; and (4) receiving a diagnosis confirmed by a gynecologist. Included patients with T2DM were followed until one of the following events occurred: (1) a diagnosis of ovarian cancer, (2) withdrawal from the NHI program, or (3) the end of the study period on December 31, 2021, as recorded in Taiwan's NHIRD.

Associated Confounders

In addition to ovarian cancer events, we considered several demographic factors and systemic disorders in our analysis and adjusted for their potential confounding effects on ovarian cancer development. These included age, urbanization level, hypertension, coronary heart disease, hyperlipidemia, cerebrovascular disease, peripheral vascular disease, endometriosis, ovarian cysts, and chronic kidney disease, with all diseases and conditions identified using *ICD-9-CM* and *ICD-10-CM* diagnostic codes. In addition, the analysis accounted for the use of certain T2DM medications, such as biguanides, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin, and statins, as identified using ATC codes. To ensure that the duration of systemic disorders and medication use was sufficient to determine whether they affected the likelihood of ovarian cancer development, only systemic diseases and medications that persisted or were prescribed for more than 2 years before the index date were included in the analyses.

Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive analyses were conducted to examine the distributions of demographic factors and systemic diseases between the 2 groups. The absolute standardized difference (ASD) was used to evaluate differences between the SGLT2 inhibitor and control groups. Subsequently, Cox proportional hazard regression was performed to calculate the adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for ovarian cancer incidence between the SGLT2 inhibitor and control groups after adjustment for all demographic factors, systemic diseases, and medication usage at baseline in the regression model. An interaction test was conducted to compare the effect of SGLT2 inhibitors on ovarian cancer development between the groups. A P value of <0.05 was considered significant, and P values less than 0.0001 were reported as $P<0.0001$.

Results

Table 1 lists the baseline characteristics of the SGLT2 inhibitor and control groups. The age distribution was similar between the groups (ASD: 0.0679). In addition, the prevalence of systemic diseases was comparable between the groups (all ASD < 0.1). The use of sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, and insulin was also similar between the SGLT2 inhibitor and control groups (all ASD < 0.1; Table 1).

Over the follow-up period of up to 6 years, 205 and 515 cases of ovarian cancer were observed in the SGLT2 inhibitor and control groups, respectively, after age matching at a ratio of 2:1 (Table 2). Furthermore, 167 and 222 cases of ovarian cancer were identified in the SGLT2 inhibitor and control groups, respectively, by using the PSM method (Table 2). The incidence of ovarian cancer was significantly lower in the SGLT2 inhibitor group than in the control group in the multivariable analysis (aHR: 0.73, 95% CI: 0.60-0.89, $P = 0.0023$; Table 3). Moreover, the cumulative probability of ovarian cancer was lower in the SGLT2 inhibitor group than in the control group after PSM ($P = 0.0026$; Figure 2). In the subgroup analysis stratified by different oral medications, 198 and 313 cases of ovarian cancer were noted in the SGLT2 inhibitor and biguanide groups, respectively (Table 4). The incidence of ovarian cancer was significantly lower in the SGLT2 inhibitor group than in the biguanide group (aHR: 0.74, 95% CI: 0.62-0.90; Table 4). In addition, the effects of SGLT2 inhibitors on ovarian cancer development significantly differed between the sulfonylurea, alpha-glucosidase inhibitor, and DPP4 inhibitor groups (all $P < 0.05$; Table 4).

Discussion

In the present study, the use of SGLT2 inhibitors in patients with T2DM was correlated with a lower incidence of ovarian cancer. In previous studies, SGLT2 inhibitor use was associated with decreased growth of certain cancer cells, such as breast and liver cancer cells [25, 26]. However, no studies have explored the correlation between SGLT2 inhibitor use and gynecological cancer development. To the best of our knowledge, this is the first study to demonstrate the protective effect of SGLT2 inhibitors on the development of ovarian cancer in the T2DM population. A clear temporal relationship between SGLT2 inhibitor use and ovarian cancer development was established by excluding patients who developed ovarian cancer within 6 months prior to initiating SGLT2 inhibitor treatment. In addition, several risk factors, including age and endometriosis, were included in the Cox proportional hazard regression to adjust for their potential effects on ovarian cancer development [19, 27]. Thus, the use of SGLT2 inhibitors is an independent protective factor for ovarian cancer. Given that SGLT2 inhibitors possess multiple functions that can counteract the mechanisms underlying ovarian cancer development [24, 28-30], their use in patients with T2DM may reduce their risk of ovarian cancer. This hypothesis is supported by the findings of the current study. On the other hand, the SGLT2 inhibitors can promote the cell cycle arrest and the apoptotic cell death of colorectal cancer cells [31]. In researches discuss the treatment potentiality of SGLT2 inhibitor on cancer, the usage of SGLT2 inhibitor can increase the responsiveness of prostate cancer to radiotherapy [32], and the SGLT2 inhibitor could serve as management for breast cancer whether as monotherapy or combination with other agents [33]. Furthermore, the application of SGLT2 inhibitors correlate to lower mortality risk of breast cancer and significantly reduced risk of prostate cancer in recent epidemiological studies [34, 35], which implied the potentiality of SGLT2 inhibitors as cancer treatment. Consequently, the protective effect of SGLT2 inhibitor on ovarian cancer development in this study could be a definitive effect rather than incidental finding. In this study, ovarian cancer occurred in 0.12% of the patients with T2DM using SGLT2 inhibitors and 0.16% of those not using SGLT2 inhibitors. The incidence of ovarian cancer in both the SGLT2 inhibitor and control groups in the present study was lower than that reported in a previous study [36]. This difference may be attributable to the effect of hyperglycemia on ovarian cancer development [20].

From an epidemiological perspective, T2DM is a prevalent disease affecting approximately 10% of the global population [3]. Furthermore, the incidence of T2DM is rising, with 700 million individuals expected to be affected by 2040 [2]. SGLT2 inhibitors, which are effective antihyperglycemic medications, are widely used in the treatment of T2DM [3, 37]. In the United States, approximately 11.2% of patients with T2DM use SGLT2 inhibitors for glycemic control [38]. In addition, ovarian cancer is the second most common gynecological cancer worldwide, after breast cancer [18]. In 2018, 240 000 individuals were given a diagnosis of ovarian cancer [18], and approximately 140 000 women die from ovarian cancer globally every year, which poses a substantial socioeconomic burden [39]. Because both T2DM and ovarian cancer affect a large proportion of the population [2, 19], exploring any potential correlations between these 2 diseases, including their management, is crucial.

This study has several limitations. First, a claims database rather than actual medical records was used for analysis. Thus, several crucial data points could not be investigated, including blood sugar and glycated hemoglobin levels in patients with T2DM, trends in these levels, medication adherence to SGLT2 inhibitors, the location and pathological details of ovarian cancer, imaging results, treatment response, recurrence of ovarian cancer, and details regarding other systemic diseases. The absent of the above crucial data could reduce the integrity and credibility of our analyses and results significantly. Second, the diagnosis of ovarian cancer was only based on the claimed codes in the NHIRD without the confirmation in histopathology, thus the accuracy of ovarian cancer diagnosis in this study may be doubted. With the solitary usage of *ICD-9-CM* (183.0) or *ICD-10-CM* (C56) codes as diagnostic criteria, whether the corresponded lesion was invasive ovarian cancer or borderline ovarian tumors cannot be confirmed. Due to the design of the Taiwan NHIRD, we can only trace one exposure-to-outcome event (i.e. SGLT2 inhibitor to ovarian cancer) in one cohort study, thus the survival data since the ovarian cancer diagnosis cannot be traced in this study. Also, smoking and obesity are known risk factors for ovarian cancer [19], but these factors are rarely documented by physicians in the claims database. Thus, we were unable to adjust for their effects in the Cox proportional hazard regression analysis. In addition, although we employed PSM to improve the comparability between the SGLT2 inhibitor and control groups, the retrospective nature of the current study may have reduced the homogeneity of the study population relative to that achievable with a prospective study. Finally, nearly all participants in the current study were Taiwanese, which may limit the external validity of the current findings.

In conclusion, this preliminary study showed that the use of SGLT2 inhibitors is associated with a lower incidence of ovarian cancer in the T2DM population, even after adjustment for several confounders. Thus, the administration of SGLT2 inhibitors can be recommended for patients with T2DM who have known risk factors for ovarian cancer. However, additional large-scale prospective studies should be conducted to evaluate the correlation between SGLT2 inhibitor use and the treatment response of ovarian cancer.

Conflicts of interest

The authors declare that they have no conflicts interests related to this study.

Funding

N/A

References

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017; 128: 40-50.

2. Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The Growing Epidemic of Diabetes Mellitus. Curr Vasc Pharmacol. 2020; 18: 104-9.

3. Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. Cardiovasc Diabetol. 2022; 21: 83.

4. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects. Int J Environ Res Public Health. 2019; 16.

5. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021; 398: 262-76.

6. Li D, Shi W, Wang T, Tang H. SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab. 2018; 20: 1972-6.

7. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol. 2020; 17: 761-72.

8. Jiang K, Xu Y, Wang D, Chen F, Tu Z, Qian J, et al. Cardioprotective mechanism of SGLT2 inhibitor against myocardial infarction is through reduction of autosis. Protein Cell. 2022; 13: 336-59.

9. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Annu Rev Physiol. 2021; 83: 503-28.

10. Sha W, Wen S, Chen L, Xu B, Lei T, Zhou L. The Role of SGLT2 Inhibitor on the Treatment of Diabetic Retinopathy. J Diabetes Res. 2020; 2020: 8867875.

11. Chung JF, Yang PJ, Chang CK, Lee CY, Huang JY, Wang K, et al. The use of sodium-glucose cotransporter 2 inhibitors and the incidence of uveitis in type 2 diabetes: a population-based cohort study. Arch Med Sci. 2024; 20: 402-9.

12. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective Effect of SGLT2 Inhibitors. Molecules. 2021; 26.

13. Yao YP, Yang PJ, Lee CY, Huang JY, Yang SF, Lin HY. Utilization of sodium-glucose cotransporter 2 inhibitors on dry eye disease severity in patients with type 2 diabetes mellitus. Int J Med Sci. 2023; 20: 1705-10.

14. Su YC, Hung JH, Chang KC, Sun CC, Huang YH, Lee CN, et al. Comparison of Sodium-Glucose Cotransporter 2 Inhibitors vs Glucagonlike Peptide-1 Receptor Agonists and Incidence of Dry Eye Disease in Patients With Type 2 Diabetes in Taiwan. JAMA Netw Open. 2022; 5: e2232584.

15. Long Q, Li L, Yang H, Lu Y, Yang H, Zhu Y, et al. SGLT2 inhibitor, canagliflozin, ameliorates cardiac inflammation in experimental autoimmune myocarditis. Int Immunopharmacol. 2022; 110: 109024.
16. Winiarska A, Knysak M, Nabrdalik K, Gumprecht J, Stompór T. Inflammation and Oxidative Stress in Diabetic Kidney Disease: The Targets for SGLT2 Inhibitors and GLP-1 Receptor Agonists. Int J Mol Sci. 2021; 22.
17. Li C, Zhang J, Xue M, Li X, Han F, Liu X, et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. Cardiovasc Diabetol. 2019; 18: 15.
18. Stewart C, Ralyea C, Lockwood S. Ovarian Cancer: An Integrated Review. Semin Oncol Nurs. 2019; 35: 151-6.
19. Roett MA, Evans P. Ovarian cancer: an overview. Am Fam Physician. 2009; 80: 609-16.
20. Wang L, Wang L, Zhang J, Wang B, Liu H. Association between diabetes mellitus and subsequent ovarian cancer in women: A systematic review and meta-analysis of cohort studies. Medicine (Baltimore). 2017; 96: e6396.
21. Zhang D, Zhao Y, Wang T, Xi Y, Li N, Huang H. Diabetes mellitus and long-term mortality of ovarian cancer patients. A systematic review and meta-analysis of 12 cohort studies. Diabetes Metab Res Rev. 2017; 33.
22. Macciò A, Madeddu C. Inflammation and ovarian cancer. Cytokine. 2012; 58: 133-47.
23. Saed GM, Diamond MP, Fletcher NM. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. Gynecol Oncol. 2017; 145: 595-602.
24. Ding DN, Xie LZ, Shen Y, Li J, Guo Y, Fu Y, et al. Insights into the Role of Oxidative Stress in Ovarian Cancer. Oxid Med Cell Longev. 2021; 2021: 8388258.
25. Komatsu S, Nomiyama T, Numata T, Kawanami T, Hamaguchi Y, Iwaya C, et al. SGLT2 inhibitor ipragliflozin attenuates breast cancer cell proliferation. Endocr J. 2020; 67: 99-106.
26. Kaji K, Nishimura N, Seki K, Sato S, Saikawa S, Nakanishi K, et al. Sodium glucose cotransporter 2 inhibitor canagliflozin attenuates liver cancer cell growth and angiogenic activity by inhibiting glucose uptake. Int J Cancer. 2018; 142: 1712-22.
27. Rooth C. Ovarian cancer: risk factors, treatment and management. Br J Nurs. 2013; 22: S23-30.
28. Xing YJ, Liu BH, Wan SJ, Cheng Y, Zhou SM, Sun Y, et al. A SGLT2 Inhibitor Dapagliflozin Alleviates Diabetic Cardiomyopathy by Suppressing High Glucose-Induced Oxidative Stress in vivo and in vitro. Front Pharmacol. 2021; 12: 708177.
29. Yang Z, Li T, Xian J, Chen J, Huang Y, Zhang Q, et al. SGLT2 inhibitor dapagliflozin attenuates cardiac fibrosis and inflammation by reverting the HIF-2α

signaling pathway in arrhythmogenic cardiomyopathy. Faseb j. 2022; 36: e22410.
30. Brieger KK, Phung MT, Mukherjee B, Bakulski KM, Anton-Culver H, Bandera EV, et al. High Prediagnosis Inflammation-Related Risk Score Associated with Decreased Ovarian Cancer Survival. Cancer Epidemiol Biomarkers Prev. 2022; 31: 443-52.
31. Anastasio C, Donisi I, Del Vecchio V, Colloca A, Mele L, Sardu C, et al. SGLT2 inhibitor promotes mitochondrial dysfunction and ER-phagy in colorectal cancer cells. Cell Mol Biol Lett. 2024; 29: 80.
32. Ali A, Mekhaeil B, Biziotis OD, Tsakiridis EE, Ahmadi E, Wu J, et al. The SGLT2 inhibitor canagliflozin suppresses growth and enhances prostate cancer response to radiotherapy. Commun Biol. 2023; 6: 919.
33. Naeimzadeh Y, Tajbakhsh A, Nemati M, Fallahi J. Exploring the anti-cancer potential of SGLT2 inhibitors in breast cancer treatment in pre-clinical and clinical studies. Eur J Pharmacol. 2024; 978: 176803.
34. Zheng J, Lu J, Qi J, Yang Q, Zhao H, Liu H, et al. The effect of SGLT2 inhibition on prostate cancer: Mendelian randomization and observational analysis using electronic healthcare and cohort data. Cell Rep Med. 2024; 5: 101688.
35. Luo J, Hendryx M, Dong Y. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and non-small cell lung cancer survival. Br J Cancer. 2023; 128: 1541-7.
36. La Vecchia C. Ovarian cancer: epidemiology and risk factors. Eur J Cancer Prev. 2017; 26: 55-62.
37. Nelinson DS, Sosa JM, Chilton RJ. SGLT2 inhibitors: a narrative review of efficacy and safety. J Osteopath Med. 2021; 121: 229-39.
38. Mahtta D, Ramsey DJ, Lee MT, Chen L, Al Rifai M, Akeroyd JM, et al. Utilization Rates of SGLT2 Inhibitors and GLP-1 Receptor Agonists and Their Facility-Level Variation Among Patients With Atherosclerotic Cardiovascular Disease and Type 2 Diabetes: Insights From the Department of Veterans Affairs. Diabetes Care. 2022; 45: 372-80.
39. Penny SM. Ovarian Cancer: An Overview. Radiol Technol. 2020; 91: 561-75.

Figure and Legend

Figure 1. Flowchart of participant selection

NHIRD: National Health Insurance Research Database, N: number, T2DM: type 2 diabetes mellitus, SGLT2: sodium-glucose cotransporter 2, PSM: propensity score matching.

Figure 2. Cumulative probability of ovarian cancer between the control group and SGLT2 group, determined using (A) 2:1 age matching and (B) propensity score matching.

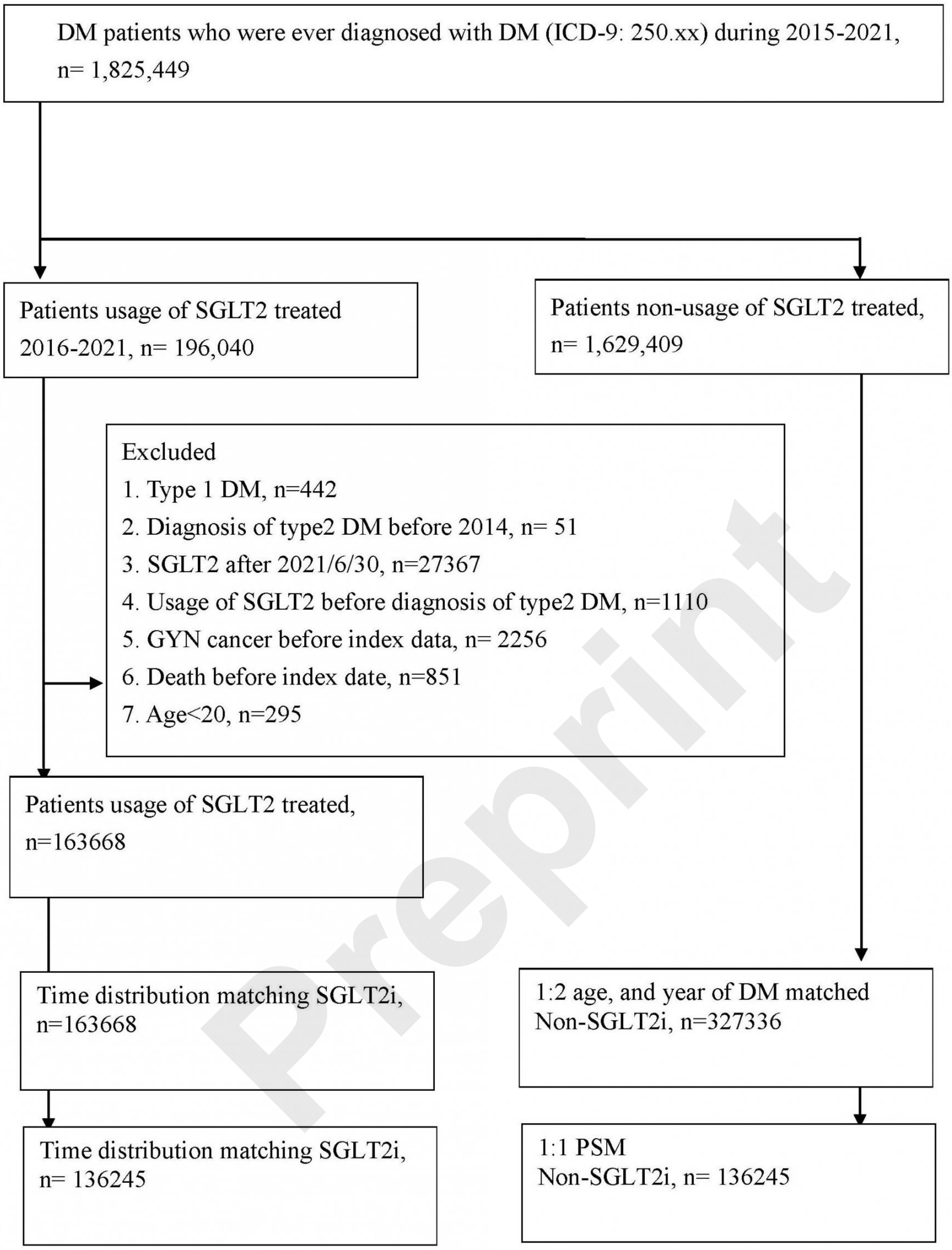

DM patients who were ever diagnosed with DM (ICD-9: 250.xx) during 2015-2021, n= 1,825,449
Patients usage of SGLT2 treated 2016-2021, n= 196,040
Patients non-usage of SGLT2 treated, n= 1,629,409
Excluded
1. Type 1 DM, n=442
2. Diagnosis of type2 DM before 2014, n= 51
3. SGLT2 after 2021/6/30, n=27367
4. Usage of SGLT2 before diagnosis of type2 DM, n=1110
5. GYN cancer before index data, n= 2256
6. Death before index date, n=851
7. Age<20, n=295
Patients usage of SGLT2 treated, n=163668
Time distribution matching SGLT2i, n=163668
1:2 age, and year of DM matched Non-SGLT2i, n=327336
Time distribution matching SGLT2i, n= 136245
1:1 PSM Non-SGLT2i, n= 136245

Table 1. Baseline characteristics SGLT-2 inhibitor users and matched comparison.

	2:1 age matching			After PSM		
	Non- SGLT2	SGLT2	ASD	Non- SGLT2	SGLT2	ASD
N	327336	163668		136245	136245	
Index year			0.0000			0.0374
2016	30482 (9.31%)	15241 (9.31%)		12810 (9.40%)	12881 (9.45%)	
2017	73150 (22.35%)	36575 (22.35%)		30498 (22.38%)	30843 (22.64%)	
2018	63814 (19.49%)	31907 (19.49%)		26639 (19.55%)	26595 (19.52%)	
2019	62864 (19.20%)	31432 (19.20%)		26055 (19.12%)	25895 (19.01%)	
2020	62004 (18.94%)	31002 (18.94%)		25630 (18.81%)	25536 (18.74%)	
2021	35022 (10.70%)	17511 (10.70%)		14613 (10.73%)	14495 (10.64%)	
Age			0.0000			0.0679
20-39	17670 (5.40%)	8835 (5.40%)		4301 (3.16%)	6057 (4.45%)	
40-49	36722 (11.22%)	18361 (11.22%)		13298 (9.76%)	14499 (10.64%)	
50-59	80116 (24.48%)	40058 (24.48%)		33510 (24.60%)	33504 (24.59%)	
60-69	111622 (34.10%)	55811 (34.10%)		49329 (36.21%)	47775 (35.07%)	
70-79	60504 (18.48%)	30252 (18.48%)		26928 (19.76%)	25850 (18.97%)	
>=80	20702 (6.32%)	10351 (6.32%)		8879 (6.52%)	8560 (6.28%)	
Mean ± SD	61.26(12.44)	61.26(12.44)		62.47(11.46)	61.70(12.10)	
Comorbidities						
Hypertension	169611 (51.82%)	101028 (61.73%)	0.2011	84263 (61.85%)	83196 (61.06%)	0.0161
CAD	30924 (9.45%)	23051 (14.08%)	0.1443	16816 (12.34%)	17354 (12.74%)	0.0119
Hyperlipidemia	167061 (51.04%)	108528 (66.31%)	0.3140	89802 (65.91%)	88631 (65.05%)	0.0181
Ischemic stroke	13958 (4.26%)	7799 (4.77%)	0.0241	6549 (4.81%)	6410 (4.70%)	0.0048
Hemorrhage stroke	2289 (0.70%)	1164 (0.71%)	0.0014	916 (0.67%)	926 (0.68%)	0.0009
Kidney disease	32156 (9.82%)	16497 (10.08%)	0.0086	13282 (9.75%)	13425 (9.85%)	0.0035
Rheumatoid arthritis	3557 (1.09%)	1449 (0.89%)	0.0204	1291 (0.95%)	1250 (0.92%)	0.0031

Systemic lupus erythematosus	736 (0.22%)	252 (0.15%)	0.0163	228 (0.17%)	205 (0.15%)	0.0042
Sicca/Sjogren syndrome	3856 (1.18%)	1471 (0.90%)	0.0276	1316 (0.97%)	1268 (0.93%)	0.0036
Ankylosing spondylitis	2489 (0.76%)	1185 (0.72%)	0.0042	983 (0.72%)	984 (0.72%)	0.0001
COPD	8539 (2.61%)	4241 (2.59%)	0.0011	3535 (2.59%)	3445 (2.53%)	0.0042
Medication						
NSAIDs	194966 (59.56%)	99533 (60.81%)	0.0256	82390 (60.47%)	82321 (60.42%)	0.0010
Corticosteroids	65684 (20.07%)	34487 (21.07%)	0.0249	28110 (20.63%)	28184 (20.69%)	0.0013
PPI	28343 (8.66%)	15088 (9.22%)	0.0196	11993 (8.80%)	12081 (8.87%)	0.0023
Aspirin	55706 (17.02%)	38670 (23.63%)	0.1648	30406 (22.32%)	30658 (22.50%)	0.0044
Statin	161792 (49.43%)	119710 (73.14%)	0.5020	96642 (70.93%)	96208 (70.61%)	0.0070
Alpha-blockers	5612 (1.71%)	2996 (1.83%)	0.0088	2435 (1.79%)	2446 (1.80%)	0.0006
Beta- blockers	86740 (26.50%)	54864 (33.52%)	0.1537	43250 (31.74%)	43578 (31.99%)	0.0052
CCBs	87183 (26.63%)	44789 (27.37%)	0.0165	38063 (27.94%)	37391 (27.44%)	0.0110
ACEI	13903 (4.25%)	9126 (5.58%)	0.0615	7141 (5.24%)	7192 (5.28%)	0.0017
ARBs	132465 (40.47%)	91676 (56.01%)	0.3149	74224 (54.48%)	73839 (54.20%)	0.0057
Biguanides	179428 (54.81%)	149456 (91.32%)	0.9028	124273 (91.21%)	122104(89.62%)	0.0541
Sulfonylureas	73873 (22.57%)	66089 (40.38%)	0.3908	51651 (37.91%)	51276 (37.64%)	0.0057
Alpha glucosidase inhibitors	22845 (6.98%)	27730 (16.94%)	0.3107	17845 (13.10%)	19280 (14.15%)	0.0307
Thiazolidinediones	23704 (7.24%)	29103 (17.78%)	0.3227	19650 (14.42%)	20621 (15.14%)	0.0201
DPP4	54086 (16.52%)	62791 (38.36%)	0.5048	41366 (30.36%)	44676 (32.79%)	0.0523
Insullin	38605 (11.79%)	39236 (23.97%)	0.3219	25793 (18.93%)	27779 (20.39%)	0.0367
GLP-1	3215 (0.98%)	3566 (2.18%)	0.0961	2576 (1.89%)	2630 (1.93%)	0.0029

COPD: chronic obstructive pulmonary disease, CAD: Coronary Artery Disease, GLP-1:Glucagon-like peptide-1

ASD: absolute standardized difference, PSM: propensity score matching.

Table 2. Incidence rate of ovarian cancer between SGLT-2 inhibitor and control groups.

	2:1 age matching			After PSM		
	Non- SGLT2	SGLT2	P value	Non- SGLT2	SGLT2	P value
N	327336	163668		136245	136245	
Follow up person months	11191912	5706341		4668860	4777068	
New case	515	205		222	167	
Incidence rate*(95% C.I.)	0.46 (0.42-0.50)	0.36 (0.31-0.41)		0.48 (0.42-0.54)	0.35 (0.30-0.41)	
Crude Relative risk (95% C.I.)	reference	0.78 (0.66-0.92)	0.0027	reference	0.74 (0.60-0.90)	0.0026
Adjusted HR* (95% C.I.)†	reference	0.71 (0.59-0.85)	0.0002	reference	0.73 (0.60-0.89)	0.0023

*Incidence rate, per 10,000 person-months

† adjusted hazard ratio, the covariates including year of index, age, Urbanization, Insurance property, aDCSI score, co-morbidities, and medication at baseline.

Table 3. Multiple Cox regression to estimate the hazard ratio of ovarian cancer

	aHR(95% CI)	
	2:1 age matching	After PSM
Study		
Non-SGLT2	reference	reference
SGLT2	0.71 (0.59-0.85)	0.73 (0.60-0.89)
Age		
20-39	reference	Reference
40-49	1.86 (1.21-2.86)	1.17 (0.67-2.05)
50-59	1.88 (1.24-2.83)	1.12 (0.66-1.91)
60-69	1.24 (0.82-1.89)	0.74 (0.43-1.27)
70-79	1.05 (0.66-1.65)	0.61 (0.34-1.10)
>=80	0.78 (0.43-1.41)	0.47 (0.22-1.02)
Urbanization		
Urban	1.08 (0.91-1.28)	1.08 (0.85-1.36)
Sub-urban	reference	reference
Rural	0.94 (0.70-1.25)	0.90 (0.62-1.33)
Comorbidity(ref: non)		
Hypertension	1.00 (0.82-1.22)	1.05 (0.81-1.36)
CAD	0.95 (0.71-1.27)	1.03 (0.72-1.47)
Hyperlipidemia	0.82 (0.70-0.98)	0.82 (0.65-1.02)
Ischemic stroke	0.76 (0.48-1.20)	0.62 (0.34-1.16)
Hemorrhage stroke	0.95 (0.35-2.58)	1.88 (0.68-5.18)
Kidney disease	0.91 (0.66-1.25)	1.02 (0.69-1.51)
Rheumatoid arthritis	1.83 (1.04-3.20)	1.22 (0.45-3.29)
Sicca/Sjogren syndrome	1.01 (0.50-2.04)	0.28 (0.04-2.00)
Ankylosing spondylitis	0.53 (0.17-1.66)	0.35 (0.05-2.46)
COPD	1.03 (0.64-1.66)	1.29 (0.72-2.31)
Medication		
NSAIDs	0.98 (0.84-1.15)	1.12 (0.91-1.39)
Corticosteroids	1.11 (0.93-1.34)	1.09 (0.85-1.39)
PPI	1.05 (0.80-1.38)	1.03 (0.71-1.49)
Aspirin	1.05 (0.85-1.29)	0.96 (0.74-1.26)
Statin	1.09 (0.92-1.31)	1.11 (0.87-1.40)
Alpha-blockers	0.73 (0.36-1.49)	0.81 (0.33-1.98)
Beta- blockers	0.98 (0.82-1.17)	0.92 (0.73-1.16)
CCBs	1.06 (0.88-1.28)	1.04 (0.81-1.32)
ACEI	0.79 (0.53-1.17)	0.91 (0.56-1.46)
ARBs	1.06 (0.88-1.28)	1.06 (0.83-1.35)

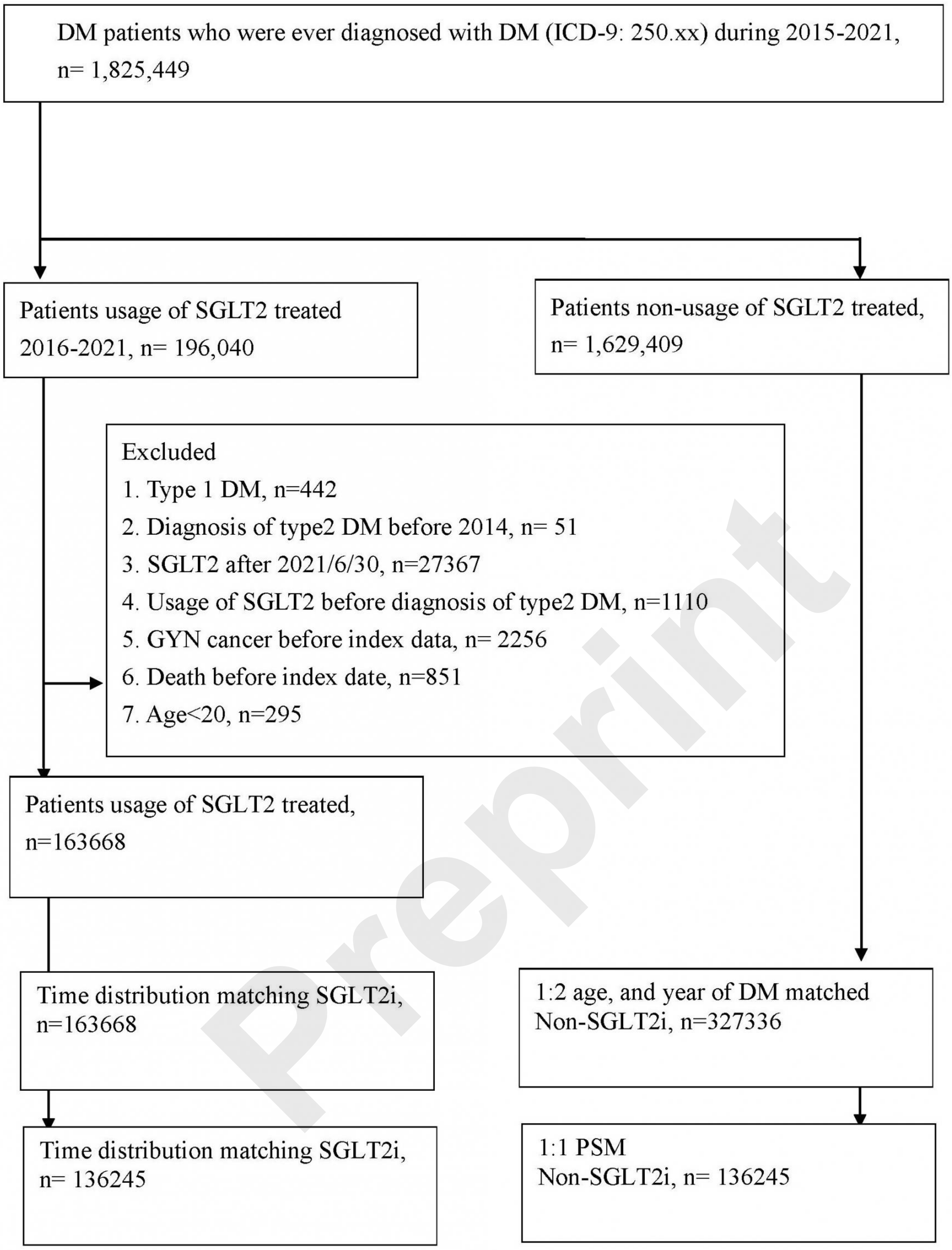
Biguanides	1.25 (1.04-1.51)	1.62 (1.03-2.54)
Sulfonylureas	1.04 (0.88-1.23)	0.97 (0.79-1.19)
Alpha glucosidase inhibitors	0.78 (0.60-1.01)	0.68 (0.49-0.95)
Thiazolidinediones	0.98 (0.77-1.26)	0.99 (0.74-1.32)
DPP4	1.19 (1.00-1.43)	1.22 (0.99-1.51)
Insullin	1.05 (0.85-1.30)	0.97 (0.75-1.27)
GLP-1	1.11 (0.61-2.03)	1.18 (0.61-2.31)

† adjusted hazard ratio, the covariates including year of index, age, Urbanization, Insurance property, aDCSI score, co-morbidities, and medication at baseline.

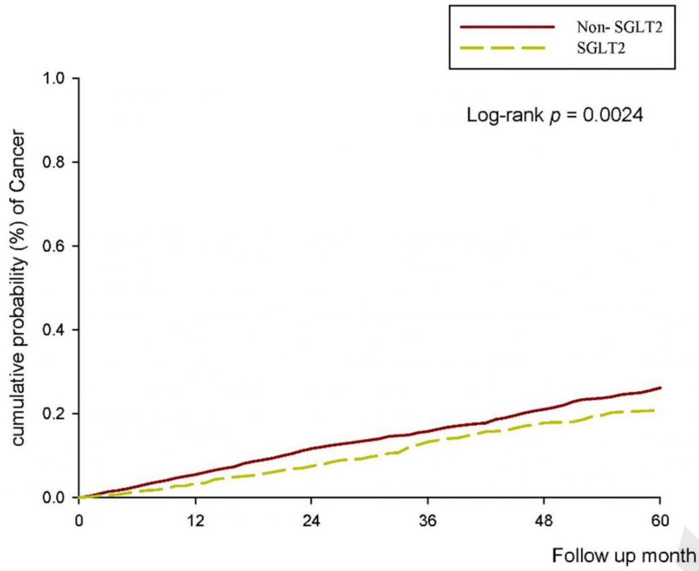
Table 4. Incidence rate of ovarian cancer by oral medications cases versus SGLT2 inhibitor cases.

	2:1 age matching	
	Biguanides	SGLT2
N	179428	149456
Follow up person months	6351636	5262944
New case	313	198
Incidence rate*(95% C.I.)	0.49 (0.44-0.55)	0.38 (0.33-0.43)
Crude Relative risk (95% C.I.)	reference	0.76 (0.64-0.91)
Adjusted HR* (95% C.I.)†	reference	0.74 (0.62-0.90)
	2:1 age matching	
	Sulfonylureas	SGLT2
N	73873	66089
Follow up person months	2701778	2347071
New case	139	79
Incidence rate*(95% C.I.)	0.51 (0.44-0.61)	0.34 (0.27-0.42)
Crude Relative risk (95% C.I.)	reference	0.65 (0.50-0.86)
Adjusted HR* (95% C.I.)†	reference	0.66 (0.49-0.88)
	2:1 age matching	
	Alpha glucosidase inhibitors	SGLT2
N	22845	27730
Follow up person months	826215	1042580
New case	36	26
Incidence rate*(95% C.I.)	0.44(0.31-0.60)	0.25(0.17-0.37)
Crude Relative risk (95% C.I.)	reference	0.57(0.35-0.95)
Adjusted HR* (95% C.I.)†	reference	0.51(0.30-0.87)
	2:1 age matching	
	DPP4	SGLT2
N	54086	62791
Follow up person months	1799628	2225113
New case	99	82
Incidence rate*(95% C.I.)	0.55 (0.45-0.67)	0.37 (0.30-0.46)
Crude Relative risk (95% C.I.)	reference	0.67 (0.50-0.90)
Adjusted HR* (95% C.I.)†	reference	0.65 (0.48-0.88)

*Incidence rate, per 10,000 person-months. † adjusted hazard ratio, the covariates including year of index, age, co-morbidities, and medication at baseline.


DM patients who were ever diagnosed with DM (ICD-9: 250.xx) during 2015-2021, n= 1,825,449
Patients usage of SGLT2 treated 2016-2021, n= 196,040
Patients non-usage of SGLT2 treated, n= 1,629,409
Excluded
1. Type 1 DM, n=442
2. Diagnosis of type2 DM before 2014, n= 51
3. SGLT2 after 2021/6/30, n=27367
4. Usage of SGLT2 before diagnosis of type2 DM, n=1110
5. GYN cancer before index data, n= 2256
6. Death before index date, n=851
7. Age<20, n=295
Patients usage of SGLT2 treated, n=163668
Time distribution matching SGLT2i, n=163668
1:2 age, and year of DM matched Non-SGLT2i, n=327336
Time distribution matching SGLT2i, n= 136245
1:1 PSM Non-SGLT2i, n= 136245

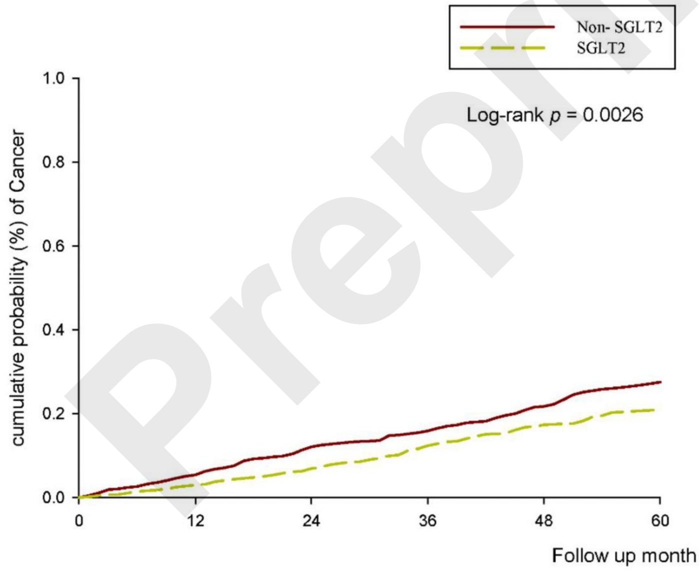
(A) 2:1 age matching



n at risk

Non-SGLT2	327336	292196	225550	161891	99543	32979
SGLT2	163668	147381	115057	83402	51971	17482

(B) After PSM



n at risk

Non-SGLT2	136245	121639	94080	67635	41657	13883
SGLT2	136245	122879	96236	70137	43903	14824